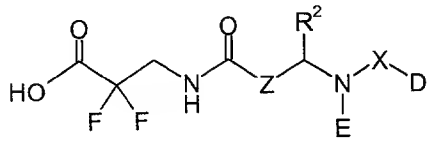
CLAIMS

1. A compound of the general formula (I):



(I)

wherein

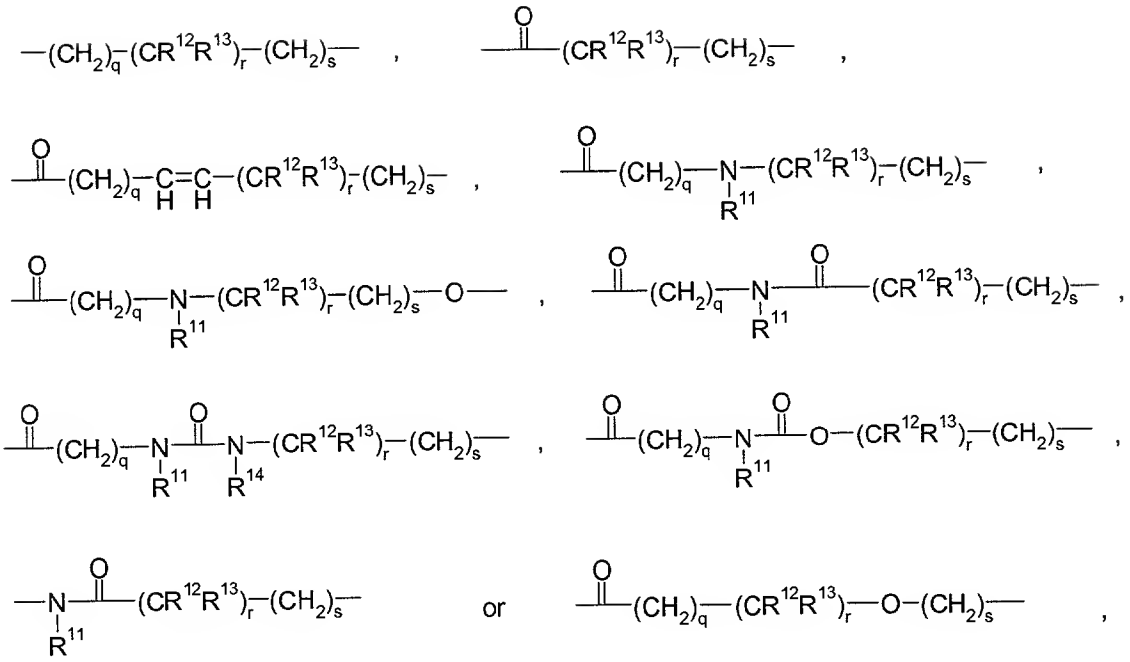
R^2 is hydrogen or C_{1-6}-alkyl,

Z is arylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^7 and R^8 selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^9$, $-NR^9R^{10}$ and C_{1-6}-alkyl,

wherein R^9 and R^{10} independently are hydrogen or C_{1-6}-alkyl,

X is



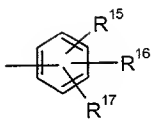
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{11}, R^{12}, R^{13} and R^{14} independently are hydrogen or C_{1-6}-alkyl,

D is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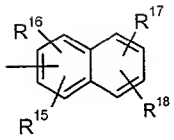
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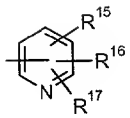
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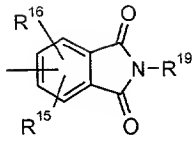
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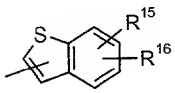
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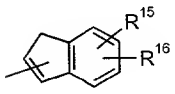
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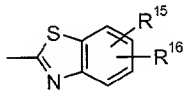
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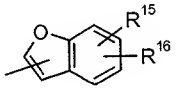
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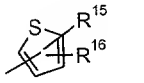
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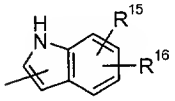
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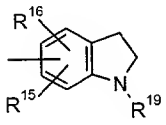
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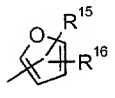
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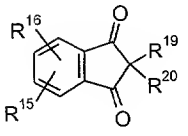

,

wherein

R^{15}, R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$, $-SR^{21}$, $-NR^{21}S(O)_2R^{22}$, $-S(O)_2NR^{21}R^{22}$, $-S(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-CH_2C(O)NR^{21}R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-CH_2OR^{21}$, $-CH_2NR^{21}R^{22}$, $-OC(O)R^{21}$, $-C(O)R^{21}$ or $-C(O)OR^{21}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio,

C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{15} to R^{18} when placed in adjacent positions together may form a bridge $-(CR^{23}R^{24})_a$-O-$(CR^{25}R^{26})_c$-O-,

wherein

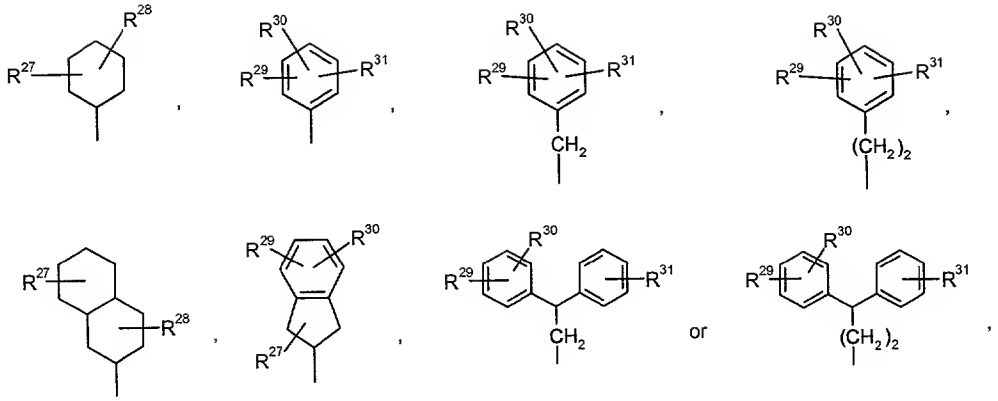
a is 0, 1 or 2,

c is 1 or 2,

R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, C_{1-6}-alkyl or fluorine,

R^{19} and R^{20} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is



wherein

R^{27} and R^{28} independently are

hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{32}$, $-NR^{32}R^{33}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl or aryl,

wherein the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{32}$, $-NR^{32}R^{33}$ and C_{1-6}-alkyl,

wherein

R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl, or

R^{32} and R^{33} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{29}, R^{30} and R^{31} independently are

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

  wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

  or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{29}, R^{30} and R^{31} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical $-O-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-S-$,

wherein

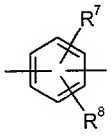
t and l independently are 0, 1, 2, 3, 4 or 5,

R^{36} and R^{37} independently are hydrogen or C_{1-6}-alkyl,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

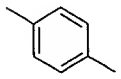
2. A compound according to claim 1, wherein R^2 is hydrogen.

3. A compound according to claim 1, wherein Z is

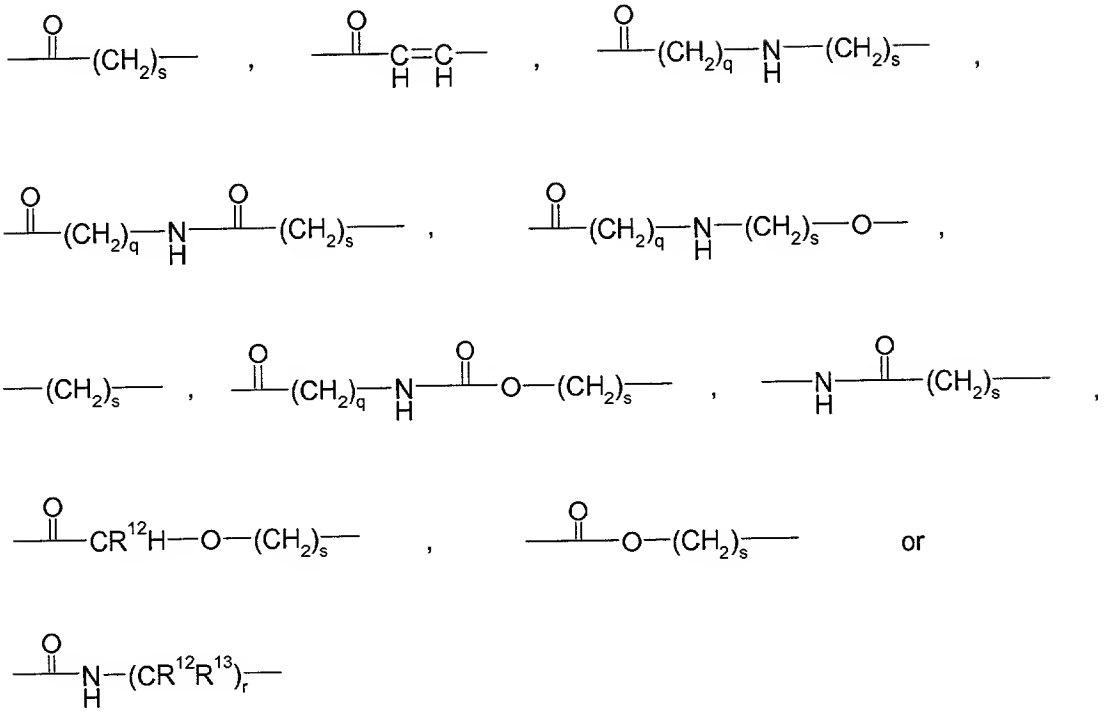


wherein R^7 and R^8 are as defined in claim 1.

4. A compound according to claim 3, wherein Z is



5. A compound according to claim 1, wherein X is



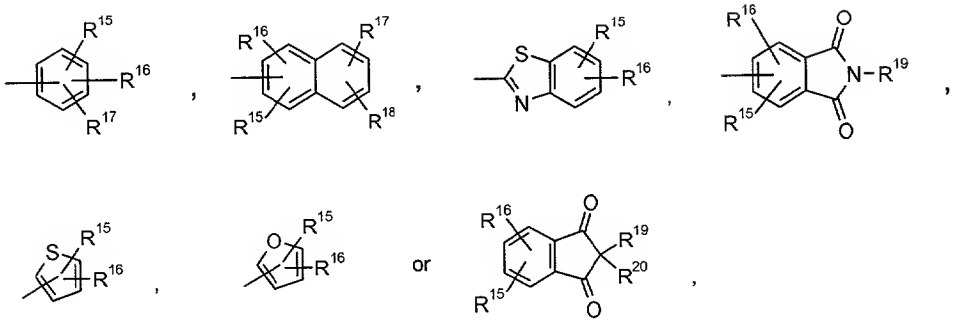
wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R^{12} and R^{13} independently are hydrogen or C_{1-6}-alkyl.

6. A compound according to claim 5, wherein X is -C(O)NH-, -C(O)NHCH$_2$-, -C(O)NHCH(CH$_3$)-, -C(O)NHCH$_2$CH$_2$-, -C(O)CH$_2$-, -C(O)CH=CH-, -(CH$_2$)$_s$-, -C(O)-, -C(O)O- or -NHC(O)-, wherein s is 0 or 1.

7. A compound according to claim 6, wherein X is -C(O)NH-, -C(O)NHCH$_2$-, -C(O)NHCH(CH$_3$)-, -C(O)NHCH$_2$CH$_2$-, -C(O)CH$_2$-, -CH$_2$-, -C(O)- or -NHC(O)-.

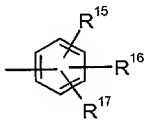
8. A compound according to claim 7, wherein X is -C(O)NH-.

9. A compound according to claim 1, wherein D is



wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} are as defined in claim 1.

10. A compound according to claim 9, wherein D is



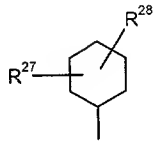
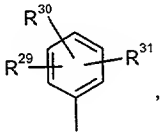
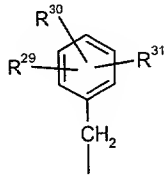
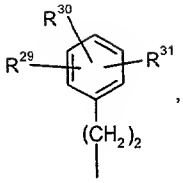
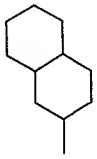
wherein R^{15}, R^{16} and R^{17} are as defined in claim 1.

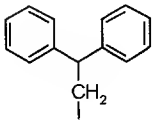
11. A compound according to claim 9, wherein R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6}-alkyl, C_{1-6}-alkoxy, $-S-C_{1-6}$-alkyl, $-C(O)OR^{21}$, $-C(O)R^{21}$, $-CH_2OR^{21}$, $-C(O)NR^{21}R^{22}$, $-S(O)_2R^{21}$, $-S(O)_2CF_3$, $-S(O)_2NR^{21}R^{22}$, C_{3-8}-cycloalkyl or aryl, or two of the groups R^{15}, R^{16} and R^{17} when placed in adjacent positions together form a bridge $-(CR^{23}R^{24})_a-O-(CR^{25}R^{26})_c-O-$, wherein R^{21} and R^{22} independently are hydrogen or C_{1-6}-alkyl, and a, c, R^{23}, R^{24}, R^{25} and R^{26} are as defined in claim 1.

12. A compound according to claim 11, wherein R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$ or C_{1-6}-alkoxy.

13. A compound according to claim 12, wherein R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, $-CF_3$ or $-OCF_3$.

14. A compound according to claim 1, wherein E is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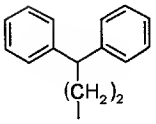
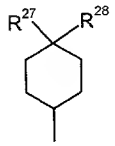


wherein R^{27}, R^{28}, R^{29}, R^{30} and R^{31} are as defined in claim 1.

15. A compound according to claim 14, wherein E is



wherein R^{27} and R^{28} are as defined in claim 1.

16. A compound according to claim 14, wherein R^{27} and R^{28} independently are

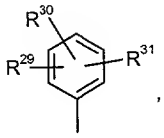
- hydrogen, C_{1-6}-alkyl,
- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl or phenyl, which may optionally be substituted as defined in claim 1.

17. A compound according to claim 16, wherein R^{27} is hydrogen and R^{28} is

- C_{1-6}-alkyl,

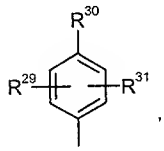
- C_{4-8}-cycloalkenyl or C_{3-8}-cycloalkyl, which may optionally be substituted as defined in claim 1.

18. A compound according to claim 14, wherein E is



wherein R^{29}, R^{30} and R^{31} are as defined in claim 1.

19. A compound according to claim 18, wherein E is



wherein R^{29}, R^{30} and R^{31} are as defined in claim 1.

20. A compound according to claim 18, wherein R^{29}, R^{30} and R^{31} independently are

- hydrogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds.

21. A compound according to claim 20, wherein R^{29}, R^{30} and R^{31} independently are

hydrogen, C_{1-6}-alkoxy, $-CF_3$, $-OCF_3$ or $-NR^{34}R^{35}$, wherein R^{34} and R^{35} are as defined in claim 1, or

C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which are optionally substituted as defined in claim 1.

22. A compound according to claim 21, wherein R^{29}, R^{30} and R^{31} independently are

hydrogen or

C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which are optionally substituted as defined in claim 1.

23. A compound according to claim 22, wherein R^{29}, R^{30} and R^{31} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, wherein C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl are optionally substituted with C_{1-6}-alkyl.

24. A compound according to claim 23, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, wherein C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl are optionally substituted with C_{1-6}-alkyl.

25. A compound according to claim 24, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{1-6}-alkyl.

26. A compound according to claim 25, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{4-8}-cycloalkenyl which is optionally substituted with C_{1-6}-alkyl.

27. A compound according to claim 1, wherein said compound has an IC_{50} value of no greater than 5 μM as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II).

28. A compound according to claim 27, wherein said compound has an IC_{50} value of less than 1 μM, preferably of less than 500 nM and even more preferred of less than 100 nM as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II).

29. A compound according to claim 1, wherein said compound is an agent useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, impaired glucose tolerance, Type 2 diabetes, Type 1 diabetes and obesity.

30. A compound according to any one of the claims 1 to 29 for use as a medicament.

31. A pharmaceutical composition comprising at least one compound according to claim 1 together with one or more pharmaceutically acceptable carriers or excipients.

32. A pharmaceutical composition according to claim 31 in unit dosage form, said composition comprising from about 0.05 mg to about 1000 mg of the compound according to claim 1.

33. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial.

34. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of glucagon-mediated disorders and diseases.

35. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of hyperglycemia.

36. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for lowering blood glucose in a mammal.

37. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of IGT.

38. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of Type 2 diabetes.

39. Use according to claim 38 for the preparation of a medicament for the delaying or prevention of the progression from IGT to Type 2 diabetes.

40. Use according to claim 38 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

41. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of Type 1 diabetes.

42. Use of a compound according to any one of the claims 1 to 29 for the preparation of a medicament for the treatment and/or prevention of obesity.

43. Use according to any one of the claims 33 to 42 in a regimen which comprises treatment with a further antidiabetic agent.

44. Use according to any one of the claims 33 to 43 in a regimen which comprises treatment with a further antiobesity agent.

45. Use according to any one of the claims 33 to 44 in a regimen which additionally comprises treatment with an antihypertensive agent.

46. A method for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

47. The method according to claim 46, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg per day.

48. The method according to claim 46, wherein the effective amount of the compound is in the range of from about 0.1 mg to about 1000 mg per day.

49. The method according to claim 46, wherein the effective amount of the compound is in the range of from about 0.5 mg to about 500 mg per day.

50. A method for the treatment and/or prevention of glucagon-mediated disorders and diseases, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

51. A method for the treatment and/or prevention of hyperglycemia, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

52. A method for for lowering blood glucose in a mammal, said method comprising administering to said mammal in need thereof an effective amount of a compound according to claim 1.

53. A method for the treatment and/or prevention of impaired glucose tolerance, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

54. A method for the treatment and/or prevention of Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

55. A method for delaying or preventing the progression from impaired glucose tolerance to Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

56. A method for delaying or preventing the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

57. A method for the treatment and/or prevention of Type 1 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

58. A method for the treatment and/or prevention of obesity, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

59. The method according to claim 46, further comprising administering an antidiabetic agent to said subject.

60. The method according to claim 46, further comprising administering an antiobesity agent to said subject.

61. The method according to claim 46, further comprising administering an antihypertensive agent to said subject.

62. A pharmaceutical composition according to claim 31 in unit dosage form, said compostion comprising from about 0.1 mg to about 500 mg of the compound according to claim 1.

63. A pharmaceutical composition according to claim 31 in unit dosage form, said compostion comprising from about 0.5 mg to about 200 mg of the compound according to claim 1.

64. A compound according to claim 27, wherein said compound has an IC_{50} value of less than 500 nM as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II).

65. A compound according to claim 27, wherein said compound has an IC_{50} value of less than 100 nM as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II).